[0010] In a recent study, x-ray fiber diffraction was used to screen Aβ aggregation inhibitors (Kirschner et al. (2008)). These studies showed that $A\beta_{17-28}$ fibril formation was not inhibited by nicotine or cotinine whereas $A\beta_{12-28}$ was, from this evidence, the authors proposed that the binding of aromatic small molecules to the histidines present in the Aβ sequence 12-16 (VHHQK) may inhibit the subsequent Aβ oligomerization and interfibril aggregation (Kirschner et al. (2008)).

BRIEF SUMMARY OF THE INVENTION

[0011] The subject invention concerns materials and methods for treating and/or preventing diseases associated with the accumulation and/or aggregation of Aβ peptide in neural tissue. In one embodiment, a method of the invention comprises administering a therapeutically effective amount of cotinine, or a pharmaceutically acceptable salt thereof, to a person or animal in need of treatment. The methods of the invention can be used to treat Alzheimer's disease (AD) and Parkinson's disease (PD). In one embodiment, the method is used to treat a person having Down's syndrome.

[0012] The subject invention also concerns materials and methods for treating and/or preventing stress disorders, such as post-traumatic stress disorder (PTSD). In one embodiment, a method of the invention comprises administering a therapeutically effective amount of cotinine, or a pharmaceutically acceptable salt thereof, to a person in need of treatment.

[0013] The subject invention also concerns compositions that comprise cotinine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or adjuvant.

[0014] The subject invention also concerns materials and methods for detecting, diagnosing, and monitoring conditions associated with accumulation of Aβ peptide in neural tissue, such as Alzheimer's disease and Parkinson's disease. In one embodiment, a method of the invention comprises administering detectably labeled cotinine to a person or animal. The level or concentration and/or location of labeled cotinine in neural tissue is then determined. The level of cotinine can be analyzed and a diagnosis made. In one embodiment, the cotinine is labeled with a radioisotope that can be detected by Position Emission Tomography (PET). Detection of labeled cotinine via PET provides for in vivo diagnosis and monitoring of a patient's condition. In one embodiment, Dementia associated with Parkinson's disease can be predicted by detection of labeled cotinine in striatum.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0016] FIG. **1** shows survival of cortical cells exposed to cotinine as assayed in an MTT assay.

[0017] FIGS. **2**A-**2**C and **2**B show cortical cells protected by cotinine as assayed in an MTT assay.

[0018] FIGS. **3**A and **3**B show cotinine inhibits Aβ oligomerization as assayed by MTT assay.

[0019] FIGS. **4**A and **4**B show neuroprotective activity of cotinine is not affected by the antagonist of the nAChR alpha-bungarotoxin and mecamylamine.

[0020] FIG. **5** shows a dot blot using antibody 6E10.

[0021] FIGS. **6**A and **6**B show a Western blot.

[0022] FIGS. **7**A-**7**C. Cotinine protects neurons against Aβ toxicity. Embryonic cortical neurons after 7 days in vitro (DIV) were treated with 5 μM Aβ either alone or with various concentrations of cotinine (0.1, 1, 10 μM). After 24 h cell viability was assessed using MTT assay (FIG. **7**A) and double calcein-AM and PI staining (FIG. **7**B). The MTT and calcein/PI staining values were normalized against control values considered 100%. The results show that even in the absence of pre-incubation with the peptide, cotinine decreased Aβ toxicity when added to the cell culture media. Scale bar=20 μm. The values represent the mean±S.E.M., with significant difference with $P<0.05$ (*), $P<0.01$ (**), $P<0.001$ (***), between vehicle mean and treated samples mean.

[0023] FIGS. **8**A-**8**C. Cotinine inhibits Aβ oligomerization. 100 μM $A\beta_{1-42}$ was subjected to oligomerization conditions in the presence or absence of cotinine (100, 200, and 500 μM) for 1-7 days at room temperature and aliquots were analyzed using the anti-Aβ antibody 6E10 by Western blot and dot-blot immunoassays after 5 and 7 days (FIG. **8**A) and by dot-blot immunoassays using 6E10 and the highly specific anti-Aβ antibody A11, after 2 and 6 days of incubation at RT (FIG. **8**B). The results clearly show that cotinine inhibits Aβ oligomerization as expressed as a decrease in the immunoreactivity for the A11 antibody and an increase in the immunoreactivity for the 6E10 antibody. FIG. **8**C: Chemical structure of cotinine (upper), and $A\beta_{1-42}$ peptide sequence used in our studies (lower).

[0024] FIGS. **9**A-**9**E. AFM analysis of the effect of cotinine on $A\beta_{1-42}$ fibrillation. A 900 nm field of $A\beta_{1-42}$ peptide incubated at concentration 1 mM for 10 days at 37° C. in the absence (FIG. **9**A) or presence (FIG. **9**B) of cotinine 2 mM. The plot represents the length of the Aβ fibrils formed under the conditions illustrated in FIGS. **9**A and **9**B. The difference in length of the $A\beta_{1-42}$ fibrils was considered significant with $P=0.0228$ (Student-t test) (FIG. **9**C).

[0025] FIG. **10**. x-ray analysis of the $A\beta_{1-42}$ after vapor-hydration of the lyophilized peptide. Intensity of x-ray scatter as a function of distance from the center of the pattern. Weak reflections, characteristics of β-sheet structure, are apparent at ~0.10 $Å^{-1}$ and 0.21 $Å^{-1}$, which correspond to the intersheet (horizontal bar) and hydrogen-bonding (arrow) reflections. The intense, broad band at 0.30-0.35 $Å^{-1}$ (w) is from water in the vapor-hydrated, lyophilized peptide. Inset, after 10 days incubation, a vapor-hydrated, lyophilized $A\beta_{1-42}$ solution shows more intense spacing from the β-conformation, suggesting the formation of more aggregates.

[0026] FIGS. **11**A-**11**D. Cotinine is neuroprotective by blocking Aβ aggregation/oligomerization. The results show the viability of 7 DIV cortical cells exposed to pre-aggregated and fresh dissolved $A\beta_{1-42}$-cotinine solutions for 24 h at 37° C. FIG. **11**A) MTT analysis of cell viability of cells treated with $A\beta_{1-42}$ solutions that were pre-incubated for 3 h at 4° C., and then added to the cell culture media containing 10 μM cotinine. FIG. **11**B) MTT analysis of the cell viability of cortical cells treated with $A\beta_{1-42}$ pre-incubated with ascending concentrations of cotinine for 3 h at 4° C. The results indicate that when cotinine is added after a pre-aggregation step of the peptide it does not protect against Aβ toxicity, but when cotinine is pre-incubated with the $A\beta_{1-42}$ solution it is able to protect against toxicity. Plots represent cell viability as percentage of vehicle-treated controls. The results were con-